Epidemiology of sarcopenia and insight into possible therapeutic targets

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Summary

Musculoskeletal aging is a major public health concern due to demographic population changes. Sarcopenia, the age related loss of muscle mass and function, is associated with significant personal morbidity and public health care costs; it is associated with falls, loss of independence in older adults, and hospitalisation with poorer health outcomes among those affected. Just as for adult bone mass, muscle mass and strength increases in late adolescence and early adulthood, but then begins to decline significantly from the age of around 50 years. In addition to the personal burden of sarcopenia there are very significant public health costs associated with the condition; in the USA these have recently been estimated to be $18.5 billion for the year 2000 alone. The aetiology of development of sarcopenia is complex, and includes loss of muscle mass, altered muscle composition, infiltration with fat and fibrous tissue and alterations in innervation. It is hoped a better understanding of these factors will help us develop strategies to counteract the problem. To date, however, methodological challenges regarding how best to define the condition, and ongoing definitional controversy, in addition to uncertainty about what outcome measures might be considered have delayed research into possible therapeutic options. Emerging pharmacological agents have largely been hormonal (testosterone and SARMs) although recent work has seen the emergence of a promising monoclonal antibody to myostatin, and ActRIIB signalling blockade as new developments.

Terms used for PubMed searches*: muscle; loss; sarcopenia; trial; therapy; drug; aging; musculoskeletal*

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Introduction

Demographic shifts in the population mean that the number of older adults in society has expanded hugely; the population aged over sixty years worldwide is predicted to rise from 841 million in 2013 to more than 2 billion by 2050. Musculoskeletal (MSK) disease is a significant burden on the aging population, contributing 7.5% of the disease burden in those over 60 years (1). The development of both osteoporosis and sarcopenia in later life (2,3) are a common problem encountered as part of musculoskeletal aging, and contribute very significantly to this burden on a personal and societal level. Research into sarcopenia has perhaps been hampered by uncertainty regarding how best to define the condition (3) (Table 1); indeed the very term sarcopenia, from the Greek meaning loss of flesh, was only first suggested in 1989 (4), and the incorporation of the concept of loss of muscle function as well as muscle mass with age has been a more recent development. However, controversy remains.

Sarcopenia is associated with a number of adverse outcomes including falls, fractures, frailty and mortality. Physical function impairment (but not multimorbidity) was predictive of mortality in older community-dwellers in the ilSIRENTE prospective cohort study (5). The physical frailty phenotype operationalized by Fried (6) predicts many of the negative outcomes described above, and indeed it is thought that muscle loss is the mediator of this association. Given the interconnection between sarcopenia and frailty, it is not surprising that there has emerged a large literature designed to identify strategies to prevent development of progression of these twin pathologies; perhaps inevitably this literature presents the case for use of biomarkers to identify those at greatest risk, although to date no single biomarker has been identified (7).

Lifestyle factors are known to be important in the prevention of sarcopenia; muscle mass and strength peak in early adulthood and subsequently decline significantly with age from approximately the fifth decade although individuals lose about 1 percent of their lean muscle mass per year after age 40. Total muscle mass decreases by nearly 50 percent for people between the ages of 20 and 90 (8). On average, people lose about 30 percent of their strength between ages 50

and 70, and another 30 percent of residual mass per decade after that. Analagous to bone loss, adoption of a more sedentary lifestyle in adolescence and young adulthood in recent years, and an extended life expectancy, might lead the reader to conclude that the prevalence of sarcopenia and associated health consequences will increase very significantly in the coming years.

How common is sarcopenia and what are the estimated costs associated with the condition?

Varying definitional approaches to sarcopenia will of course impact upon the prevalence estimates of the condition; figures have been quoted as ranging from 9% to 18% in individuals over 65 years of age, rising further to 30% in men over 80 and even higher in hospitalised patients (8,9). This is because in individuals over the age of 50 years, muscle mass is lost at a rate of 1-2% per year and strength at a (slightly greater) rate of 1.5-3% per year (10). As alluded to previously, definitions of sarcopenia have only recently been proposed and are still not fully accepted. If we apply these approaches to community dwelling cohorts such as the UK based Hertfordshire Cohort Study, a prevalence of 4.6% and 7.9% can be demonstrated among men and women respectively at a mean age of 67 years (11).

Unlike for osteoporosis, where the clear consequence of the condition is fragility fracture, the outcome associated with sarcopenia that is important and quantifiable in public health terms is much harder to define. Loss of independence is clearly important; it has been suggested that while loss of 30% of reserve capacity limits normal function, a loss of 70% results in system failure (12). This has been demonstrated in studies that illustrate that sarcopenia predicts loss of independence for activities of daily living in older men and women (13,14); for example, ability to walk (which may be limited by sarcopenia) is associated with increased healthcare costs (15), and sarcopenia is associated with a higher risk of falling, which leads to loss of independence and hospitalisation costs (16). Sarcopenia is also a predictor of poor outcomes in patients who are undergoing surgery or have other serious co-morbidities (17-19).

One of the very few studies that tried to estimate the economic costs associated with sarcopenia in the US reported an estimate of $18.5 billion ($10.8 billion in men and $7.7 billion in women) for direct costs in 2000, accounting for about 1.5% of total health expenditure in the US (20). These costs are due to hospitalisation, nursing home admissions and home healthcare expenditure, and there is an important research agenda to quantify more recent estimates, in US and elsewhere in the world, perhaps attempting to put an estimate on the indirect costs outlined above. Given that sarcopenia may also be associated with other healthcare costs such as lack of productivity, reduced quality of life and psychological problems, research in this area is also timely, especially given the recent development of a quality of life tool specifically designed for sarcopenia (21).

Definitional approached to sarcopenia

There remains considerable ongoing international debate regarding the best approach to take in the definition of sarcopenia, due in part to different technologies that might be available to inform any definition (DXA or bioimpedance for example). The International Osteoporosis Foundation and European Society for the Clinical and Economic aspects of Osteoarthritis and Osteoporosis have recently contributed to this debate through publication of a Consensus statement, and their summary is displayed in Table 1 (2,3). The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project has used data from nine sources of community dwelling older persons from the US, Iceland and Europe to also inform this debate. Among a pooled sample of 26,625 participants (57% women, mean age in men 75.2 (SD 6.1) years and in women 78.6 (SD 5.9) years), analyses recommended cut points for grip strength of <26kg in men and <16kg in women, and for low lean mass, appendicular lean mass adjusted for body mass index of <0.789 in men and <0.512 in women (22). This report also highlights numerous research priorities, specifically the evaluation of the clinical impact of a less stringent definition, epidemiological data reporting rates of change in lean mass over time, and a strong research agenda around interventions (lifestyle and pharmacological) that may retard muscle loss.

Interestingly, similar cut points for grip strength (<27kg in men, < 16kg in women) have been reported from a recent work taking a life course approach to describing grip strength using normative data from 12 British studies (49,964 participants), suggesting that consensus may be starting to develop with regard to definitional approaches (23).

One of the most recent contributions has been the Asian working group for sarcopenia, that recommends cutoff values for muscle mass measurements (7.0 kg/m^2 for men and 5.4 kg/m^2 for women by using dual X-ray absorptiometry, and 7.0 kg/m^2 for men and 5.7 kg/m^2 for women by using bioimpedance analysis), handgrip strength (<26 kg for men and <18 kg for women), and usual gait speed (<0.8 m/s) (24).

Biology of aging

Muscle cells are likely to be influenced by fundamental processes of aging that affect all living cells. These include replicative senescence and impaired stem cell regeneration; accumulation of cell damage; autophagy (reduced clearance of cell damage) and reduced mitochondrial energy generation. A full discussion of the biology of aging as applied to muscle is outside the scope of this review, and has been recently undertaken by others (25-28). However, understanding of the aetiology of age related muscle loss is of course key in the development of therapeutic strategies to retard or prevent muscle loss, and research in this field is key(29). Sarcopenia involves negative protein turnover, characterised by reduction of myofibrillar and mitochondrial protein synthesis (25) and increased proteolysis by the UPS and calcium-dependent activation of proteases. Because mitochondria are very important in energy provision, redox homeostasis and regulation of cell death, many recent articles have focused on age-related alterations of mitochondrial function in the aetiology of sarcopenia. For example, one recent review (26) postulates that defective redox signalling may be important in reducing the integrity of the aging neuromuscular system, and a better understanding of the causes of defective homeostasis provides an opportunity to identify targeted interventions. A second review, published in 2016 (27) highlights the progressive reduction in the regenerative capacity of the skeletal muscle stem

cells (satellite cells) which are critical for repair to muscle trauma or damage. Decreased capacity for muscle regeneration and increased apoptosis may be important, an assertion supported by the observation that apoptotic signalling correlates with slow walking speed and reduced muscle volume (28). Skeletal atrophy with aging is accompanied by loss of muscle strength (30) and neuromuscular impairment (loss of motor units and loss of motor neurons). Finally the therapeutic opportunities of a better understanding of the interplay between satellite cell extrinsic and intrinsic factors in sarcopenia are highlighted, and also discussed in a 2015 review by Blau et al (31).

Systemic inflammation may be important in the pathogenesis of muscle loss in later life; increased production of proinflammatory cytokines may affect all the mechanisms outlined above. 'Inflammaging' was first proposed as a phenomenon in 2000, as a possible underlying cause of muscle loss (32). Inflammaging may result from lifetime exposure to both clinical and sub-clinical infections as well as exposure to non-infective antigens leading to high antigenic load (33). An inflammatory response is mounted, leading to tissue damage and the production of reactive oxygen species which result in the release of additional cytokines (34). This vicious cycle favours a chronic pro-inflammatory state. (35,36), and might also be amenable to therapeutic manipulation.

Lifestyle modification to improve muscle mass and function

Of course, just as for bone loss, a factor that is important in affecting muscle may influence either development of peak mass, or rates of loss, or indeed a combination of both factors, and the peak attained in youth may be an important determinant of function in later life, and will be affected by environmental and genetic factors, with environmental factors potentially amenable to modification. Grip strength over the life course is illustrated in Figure 1. Genetic factors are major contributors to muscle strength, and sarcopenia is expected to also be affected by genetic factors (10). To date, the research performed to date in this area has pinpointed the myostatin pathway and the vitamin D receptor gene (10).

Before considering pharmaceutical interventions it is helpful to consider the lifestyle factors that influence muscle mass in later life, and which might be reviewed with good effect (Table 2). As we age, body fat increases and muscle mass decreases, often with relative overall stability in body weight, leading to the term sarcopenic obesity, which represents the coexistence of sarcopenia and obesity, and describes a disproportion between the amount of lean mass relative to fat mass. The varying definitions of sarcopenia, and obesity (although most studies use BMI, some studies have relied on percent body fat or visceral fat) the prevalence of sarcopenic obesity has been quoted as ranging from 0% to 41% in older populations (37). The loss of lean mass and increase in fat mass with advancing age may share common etiologic pathways and increases in fat mass and accompanying increases in adipokines and inflammation may further adversely affect muscle quality. The importance of research in this area was highlighted in a recent review of the condition (37).

Although obese or overweight adults often have a higher muscle mass compared to their non-obese peers, their lean mass is low compared to their total weight (38). Significant weight loss is associated with rapid loss of grip strength, possibly reflecting coexisting comorbidity that acts as a confounder (39). Physical activity is known to be very important in affecting muscle mass and strength. Inactivity has been shown to lead to loss of muscle mass and strength at any age. Bed rest studies have shown that a decrease in muscle strength occurs before a decrease in muscle mass (40). By contrast lifelong physical exercise has been shown to preserve muscle structure and function (41). Specifically, increases in mid-life leisure time physical activity has been shown to reduce the risk of mobility impairment in older adults, though interestingly occupational physical activity in mid-life may actually have a detrimental effect on mobility at older age (42). A recent systematic review also highlighted the studies that have suggested benefits of exercise on muscle health in later life (43); a recent review by Law et al (44) provides an overview of the evidence for the role of resistance exercise in the prevention and treatment of sarcopenia, and highlights certain critical factors- namely exercise intensity, volume and progression- that are key to optimizing the resistance exercise prescription.

Cigarette smoking may have direct effects on muscle as well as be associated with other detrimental lifestyle factors. The relationship was recently considered in the Minos study (45) where current smokers were shown to have lower appendicular muscle mass than non-smokers, and a dose-effect relationship was apparent. By contrast some other studies have reported no association (46). Alcohol consumption may also impact muscle health. While moderate alcohol intake was not associated with muscle mass in the Minos study (45), it might be anticipated that heavy alcohol consumption is likely to lead to low muscle mass through associated effects on poor nutrition, low levels of physical activity and hormonal abnormalities.

Finally, dietary factors may also be helpful for maintenance of muscle mass and strength. We know that the rate of muscle protein synthesis may be reduced by 30% in older people, as a result of poor nutrition, disease or reduced physical activity rather than aging itself (47) as well as decreased muscle protein synthesis per se, particularly in specific muscle fractions such as mitochondrial proteins (48). In a recent review of nutritional factors and muscle health by the International Osteoporosis Foundation (49), studies that showed that protein intake is positively associated with preservation of lean bone mass in men and women aged 70-79 years were reported. In most supplementation studies protein supplementation has been combined with resistance training, although the results of these trials have been mixed (50). An ESCEO consensus statement has recently considered the available evidence and recommended an optimal dietary protein intake of 1.0 to 1.2g/ kg body weight/day with at least 20-25g of high-quality protein at each main meal in post-menopausal women for prevention of age-related deterioration of musculoskeletal health (48).

Vitamin D status is topical in all areas of musculoskeletal aging, and low vitamin D levels have been associated with poorer balance and an increased risk of falls (51). A raised PTH level often accompanies low vitamin D levels, and has also been associated with sarcopenia and risk of falling independent of 25(OH)D status (52), such that recent guidance recommends an adequate vitamin D intake of

800IU/daily to maintain serum 25(OH)D levels >50 nmol/l in post-menopausal women (52).

A systematic review published in 2014 reported moderate quality evidence that exercise interventions improve muscle strength and physical performance while the benefits of nutritional interventions were more equivocal (53).

Possible therapeutic targets

When considering the selection of patients who might enter studies of novel therapies to prevent or retard development of sarcopenia, it is helpful to be aware of the regulatory processes surrounding drug development. The IOF recently published recommendations specifically addressing this issue (54), and highlight the notion that prevention of sarcopenia in high-risk pre-sarcopenic individuals could be possible, as might treatment of individuals in whom sarcopenia has already developed. The anabolic and catabolic signalling pathways that might be targeted in any therapeutic manipulation are shown in Figure 2.

Potential regulators that might be targeted to impact muscle loss include androgens (which act through the androgen receptor/Wnt/beta-catenin signalling pathway), insulin and insulin growth factor 1 (which regulate protein synthesis and degradation through the PI3K/AKT pathway), myostatin (which inhibits muscle growth), other members of the transforming growth factor beta superfamily, and inflammatory modulators including pro-inflammatory cytokines such as tumour necrosis factor-alpha and interleukin-1.

Hormonal manipulation of some kind had formed the basis of many of the studies performed to date. Testosterone supplementation is known to increase skeletal muscle volume by promoting hypertrophy of myofibers, but is associated with significant side effects, and translation to benefits on muscle function has been less clearly demonstrated. Relevant to this review, Atkinson et al trialled transdermal testosterone gel (50mg) or placebo gel daily for 6 months in a group

of thirty intermediate-frail and frail elderly men aged 65-89 years who were known to have low to borderline low testosterone, demonstrating a rise in testosterone from 11.6 (SD 3.5) to 18.0 (SD 8.1) nmol/l in the intervention group, coupled with a preservation of muscle thickness in the intervention group, compared with a decrease in the placebo group (55). Phase two trials have also been performed of an androgen receptor modulator (enobosarm), demonstrating a dose-dependent increase in total lean body mass, in addition to improvements in physical function (56). Administration of this orally administered bioavailable nonsteroidal SARM did not appear to be associated with an increased risk of adverse effects and the study group consisted of both male and female participants in their seventh decade. Reports of a trial using another selective androgen receptor modulator (MK-0773) were published in 2013 (57); in this study 170 women with sarcopenia were randomised in a double blind placebo controlled trial that demonstrated a statistically significant increase in lean body mass in the treatment group at 6 months, without evidence of androgenisation, and although physical performance also improved over follow up this was not statistically significant from the placebo treated group. The treatment group was noted to feature several patients with elevated transaminases but this resolved on study discontinuation.

Recent work has suggested that a humanised monoclonal myostatin antibody that bonds and neutralises myostatin may increase lean mass and may also improve functional measures of muscle power (58). A proof of concept double blind placebo controlled phase two trial was conducted in 201 patients aged 75 years or older who had fallen in the last year reported a difference of 0.43kg (95% CI 0.192 to 0.660); significant differences in stair climbing time, chair rise with arms and fast gait speed were also observed between the two groups over 24 weeks (58). This follows previous approval for this therapy for the treatment of inclusion body myositis in whom a single dose of therapy resulted in an increase in 6-metre walking distance of 52 metres over placebo (59).

In further work involving myostatin, it has been suggested that because postnatal blockade of the activin type IIB receptor (ActRIIB) leads to rapid and massive muscle hypertrophy, it may be a promising therapeutic target. The receptor is a

transmembrane kinase receptor highly expressed in mammalian skeletal muscle that mediates signalling for myostatin. Therapeutic approaches have involved the systemic delivery of neutralising antibodies against the receptor or mysostatin, and injection of a soluble recombinant form of the receptor that acts as a decoy disputing the interaction of endogenous receptor with its ligands (60) Having previously been trialled in patients with muscular dystrophy, a recent study of the effect of receptor blockade in wild type mice demonstrated that 8 week ActRIIB blocade with soluble receptor increased absolute force-generating capacity and reduced mitochondrial function in glycolytic gastrocnemius muscle but that this reduction did not compromise energy status during sustained activity (60).

That preventative and therapeutic strategies are required in the management of sarcopenia was the thesis of an article by Marzetti et al (61); they specifically consider mitochondrial dysfunction, highlighting the potential challenges and risks of such a study, as well as suggesting possible study populations. Unfortunately, to date no such agent is available for trial.

Conclusion

Our aging population means that conditions that emerge later in life and are associated with very significant personal and public health costs are of great significance. Sarcopenia and the linked condition frailty is perhaps one of the most significant of these. There has recently emerged a strong research agenda considering the aetiological factors that might prevent or retard the development or progression of sarcopenia. In the context of muscle aging, an understanding of the biology of aging as applied to muscle may help us to identify those at risk of sarcopenia, and to identify potential therapeutic targets, and a partnership between basic biologists, the pharmaceutical industry and clinicians seems critical. Given the very significant personal, societal and economic burdens associated with sarcopenia, it is essential that we identify ways to identify those at greatest risk, and use lifestyle strategies to retard or prevent muscle loss at a whole population approach. However, many individuals are likely to benefit from a tailored pharmacological approach in addition and while methodological challenges regarding how best to define the condition, and what outcome measure might be

considered have delayed research into possible therapeutic options, promising pharmacological agents have emerged. To date these have largely been hormonal (testosterone and SARMs) although recent work has seen the emergence of a promising monoclonal antibody to myostatin.

A particular challenge for clinicians who treat patients with the condition is that while tools have been developed that have been demonstrated to be accurate and reliable in research settings, many are not easily applied to clinical practice, and more simple tools have recently been proposed, in an attempt to facilitate incorporation of the research agenda into clinical practice [62-64]. A particular criticism of a mass based definitional approach to the condition is the relationship between loss in muscle strength and its relationship to muscle loss. While it has been demonstrated that the two are correlated, and indeed that sarcopenia predicts adverse functional outcome, loss of muscle strength often exceeds muscle loss. This is of very considerable relevance when considering definitional approaches – and clinical outcomes for pharmacological trials – analogous to bone mineral density and fracture risk, if it is functional performance that we seek to preserve, study designers should be cogniscent of the clinical outcome of choice.

Competing interests

Professor Cyrus Cooper has received consultancy fees and honoraria from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. Professor Dennison has received speaking fees from Lilly. Professor Aihie Sayer has no conflicts to declare.

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Table 1

Diagnostic criteria for sarcopenia: suggested approaches (modified from [3])

Study group	Definition	Criteria
ESPEN Special Interest Groups	"Sarcopenia is a condition characterized by loss of muscle mass and muscle strength. Although sarcopenia is primarily a disease of the elderly, its development may be associated with other conditions that are not exclusively seen in older persons, like disuse, malnutrition and cachexia. Like osteopenia, it can be also be seen in those with inflammatory diseases."	1. Low muscle mass, e.g. percentage of muscle mass >2 SDs below mean in individuals aged 18–39 y in the NHANES III cohort 2. Walking speed <0.8 m/s in the 4-min test or reduced performance in any functional test used for the comprehensive geriatric assessment
European Working Group on Sarcopenia in Older People	"Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death." The condition is called primary sarcopenia when the cause is aging per se, and secondary sarcopenia when disease, inactivity, or malnutrition contribute	1. Low muscles mass 2. Low muscle strength (e.g. grip strength) 3. Low physical performance (e.g. gait speed) Reference population of healthy young subjects using cutoff points <2 SDs below mean. Criterion 1 and Criterion 2 or 3.
International Working Group on Sarcopenia	"Sarcopenia is defined as the age-associated loss of skeletal muscle mass and function. The causes of sarcopenia are multifactorial and can include disuse, altered endocrine function, chronic disease, inflammation, insulin resistance, and nutritional deficiencies. While cachexia may be a component of sarcopenia, the two conditions are not the same."	1. Gait speed <1 m/s 2. Objectively measured low muscle mass, e.g. appendicular mass relative to height squared, i.e. ≤7.23 kg/m^2 in men and ≤5.67 kg/m^2 in women
Society of Sarcopenia, Cachexia and Wasting Disorders	"Sarcopenia with limited mobility is a specific condition with clear loss of muscle mass and a clear target for intervention. As such it	1. Walking speed ≤1 m/s or walking distance <400 m during a 6-min walk 2. A lean appendicular mass corrected for height squared of

	differs from the more general concept of frailty." "The limitation in mobility should not be clearly attributable to the direct effect of specific disease, such as peripheral vascular disease with intermittent claudication, or central and peripheral nervous system disorders (such as stroke, Parkinson's disease, spinal cord disease, or motor neuron disease), dementia, or cachexia."	>2 SDs below the mean of healthy persons aged between 20 and 30 y of the same ethnic group
Foundation for the National Institutes of Health Sarcopenia Project (FNIH)	"Low muscle mass and weakness are common and potentially disabling in older adults, but in order to become recognised as a clinical condition, criteria for diagnosis should be based on clinically relevant thresholds and independently validated. Based on a pooled sample of 26,625 participants, final recommended cutpoints for weakness and low lean mass are presented. "	ALM adjusted for BMI – men<0.789; women<0.512 Grip strength – men<26kg; women<16kg Gait speed <=0.8 m/s
Asian working group for sarcopenia	'sarcopenia should be described as low muscle mass plus low muscle strength and/or low physical performance, and we also recommend outcome indicators for further researches, as well as the conditions that sarcopenia should be assessed'.	Cutoff values for muscle mass measurements: 7.0 kg/m^2 for men and 5.4 kg/m^2 for women by using dual X-ray absorptiometry, and 7.0 kg/m^2 for men and 5.7 kg/m^2 for women by using bioimpedance analysis, handgrip strength handgrip strength (<26 kg for men and <18 kg for women) usual gait speed (<0.8 m/s)

Table 2

Risk factors for muscle aging (adapted from [46])

Constitutional	**Lifestyle**
	Low body weight
Age	Cigarette smoking
	Excessive alcohol consumption
Sex hormone deficiency	Prolonged immobilisation
Early environment	
	Low protein intake
Co-morbidity	Vitamin D deficiency
Genetic Factors	Use of ACE inhibitors
	Use of steroids
	Low growth hormone level

Figure 1. Reference data for grip strength across the lifecourse in the HALCyon Consortium: 14 cohorts. Reproduced with permission from *Dodds R et al PLOS One 2014; 9: e113637*

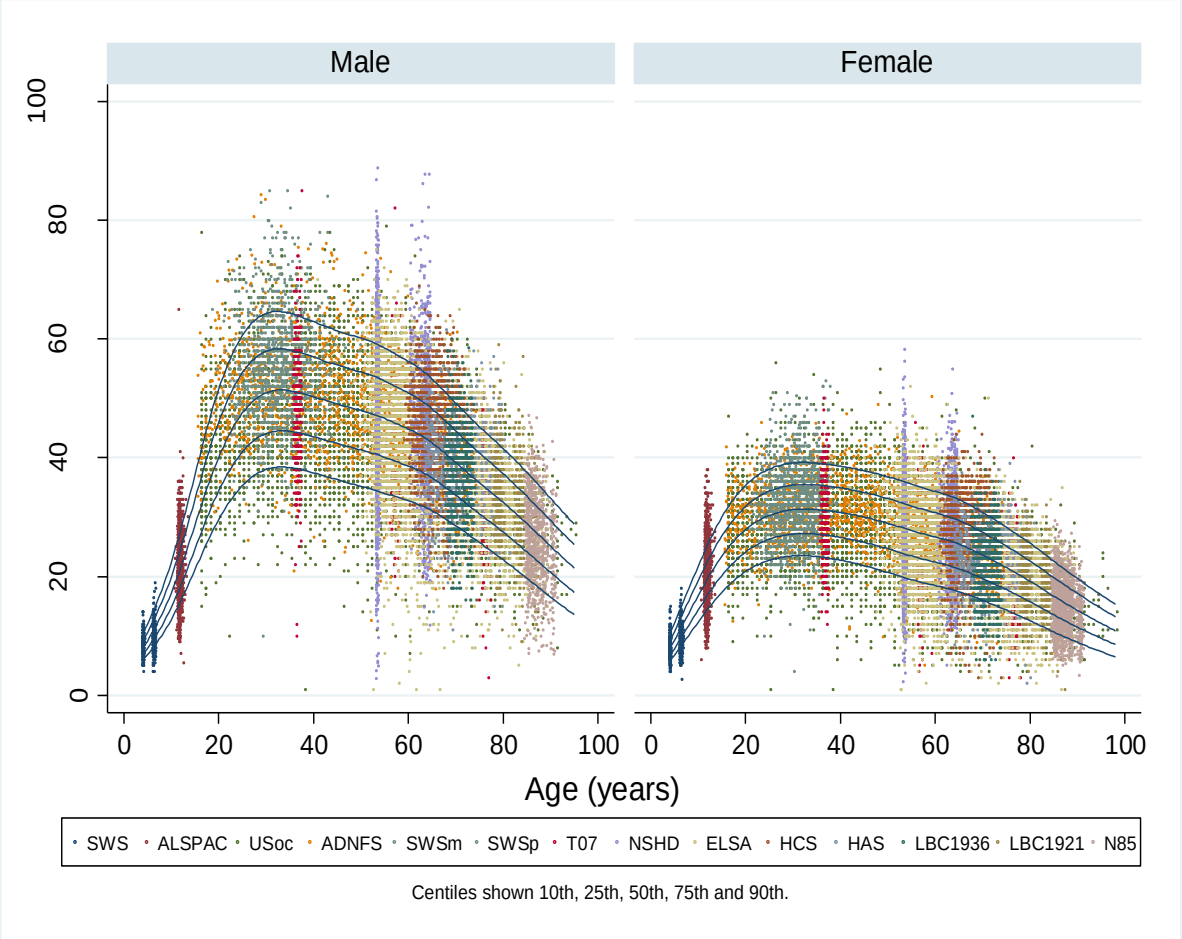
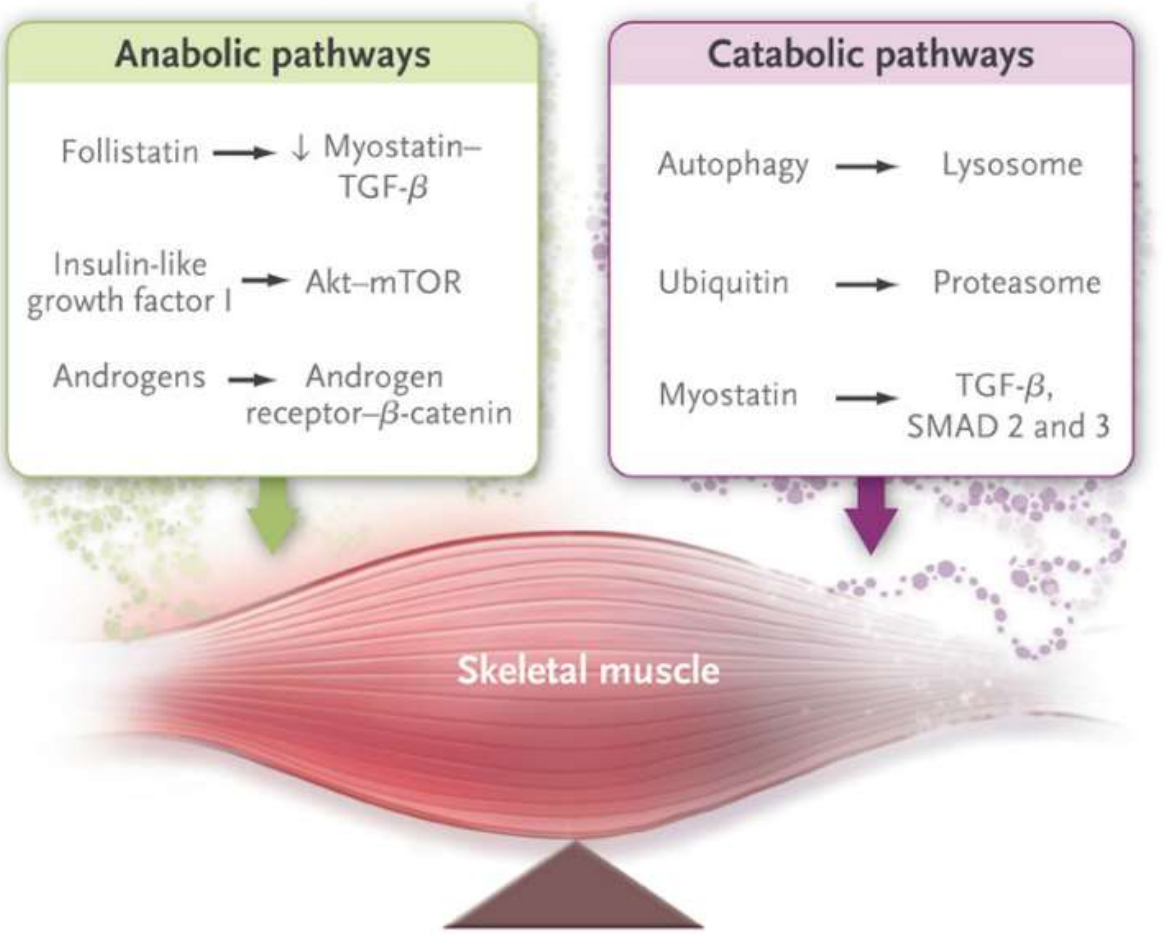


Figure 2. Anabolic and catabolic signalling pathways in muscle



Androgens, GH mimetics & follistatin – anabolic pathways Myostatin & ubiquitin ligases - catabolic pathways